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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/164,862	10/01/1998	PAUL A. PRICE	023070-08672	7170

22798 7590 04/15/2003

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/15/2003

37

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/164,862	Applicant(s) Price et al
	Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 19, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18, 38, 39, 49-51, and 54-62* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-18, 38, 39, 49-51, and 54-62* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on October 7, 2002 (Paper No. 33) and February 19, 2003 (Paper No. 36) have been entered. Claims 1-18, 38-39, 49-51, 54-62 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

New Grounds of Objection

Specification

4. The specification is objected to because it recites that a breast cancer study is disclosed in Johansen et al (1993, Brit. J. Rheum, 32:949-955), see p. 45, lines 12-17. A review of the art of record reveal that the breast cancer study is actually in European J. Of Cancer, Vol 31A, No. 9, pp. 1437-1442. Amendment of the specification to make appropriate correction is required.

5. The use of the trademarks in the specification has been noted in this application, in particular on p. 63, line 29, p. 66, line 29. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to

prevent their use in any manner which might adversely affect their validity as trademarks.

Each letter of the trademarks must be capitalized. See MPEP 608.01(V) and Appendix I.

Examiner has made an effort to identify wherein all of these informalities may occur. However, Applicant is required to review the specification and make appropriate correction.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

6. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

7. Claims 38-39 are rejected under 35 USC 101 because the disclosed invention is inoperative and therefore lacks utility.

The claims are drawn to a method to screen for recurrence of a cancer comprising measuring levels of YKL-40 in a sample from a cancer patient, wherein a statistically significant difference in YKL-40 level in the sample compared to a sample from a normal healthy mammal indicates the presence of a cancer. The claims are inoperative because it is not possible to determine the statistical significance of two single samples.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

9. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for estimating survival expectancy of a cancer patient comprising obtaining a biological sample comprising YKL-40 from a cancer patient, wherein thirty-one different cancer types are claimed, measuring the level of YKL-40 in said sample and comparing the level to the YKL-40 level found in the same sample from a normal healthy human wherein a sample YKL-40 level in excess of YKL-40 levels in the same sample from a normal healthy human indicates a reduced survival expectancy compared to patients with normal YKL-40 level. The claims are drawn to predicting survival expectancy.

The specification teaches that serum levels of YKL-40 were measured in a clinical group of 60 breast cancer patients (p. 45, lines 10-19), 47 of which entered the study at the time that breast cancer recurrence was first suspected, 6 of whom did not have breast cancer recurrence, 6 had locally advanced disease or distant

metastasis at the time of initial breast cancer diagnosis and 7 entered the study after recurrence (p. 26, lines 25-31). Data indicated that a serum YKL-40 level elevated above the 95% level of 120 normal women, correlates to decreased survival in patients with breast cancer (pgs 46-47).

Further, the specification exemplifies a study of serum YKL-40 and colorectal cancer wherein both male and female patients underwent large bowel resection for colorectal cancer (p. 51, lines 6-18) wherein the control samples were taken from persons who were healthy. The number of patients with YKL-40 levels above the age corrected 95th percentile of normal controls was 159, wherein the level is 247 ug/L wherein a significant correlation of serum level with age was found (p. 52, lines 1-12). A strong association was found between short survival and high preoperative YKL-40 levels and there was a significant relation between serum YKL-40 and Dukes' stage. The specification teaches that "If preoperative high levels of YKL-40 **do prove** (emphasis added) to identify patients in Dukes' B and C with a high risk of recurrence, more intensive follow-up and treatment could be given to these patients". Further, the specification teaches that the source of YKL-40 which lead to elevated serum levels of protein in some colorectal cancer patients is not known but could arise from secretion by the tumor cells themselves, from secretion by inflammatory cells and from normal cells in areas of the colon adjacent to tumor (p. 55, lines 14-19). In addition, preliminary data investigating the expression of YKL-40 in colon cancer biopsies show that some cancers stain intensely for YKL-40 while others are completely negative (p. 55, lines 14-19). If elevated levels of serum YKL-40 do primarily reflect secretion from a subset of

colorectal tumors, then the poor prognosis of patients with elevated serum YKL-40 suggests that YKL-40 expression may be associated with the ability of a tumor cell to invade normal tissues and to metastasize to distant sites (para bridging pages 55-56). The endpoint of the study was death of all causes (p. 52, line 28).

Further, the specification exemplifies the elevation of YKL-40 levels in prostate cancer wherein a pilot study was established to determine whether YKL-40 is elevated in prostate cancer with the ultimate goal of measuring serum YKL-40 in longitudinal studies of patients with prostate cancer in order to determine the precise relationship between YKL-40 levels and survival, wherein 8 of 20 patients have serum YKL-40 levels above 247 ug/L, Based on these results, analysis will be undertaken of serum YKL-40 from past longitudinal studies of patients in which survival is known (p. 56, lines 16-27).

The specification exemplifies the elevation of YKL-40 levels in small cell lung carcinoma patients wherein 40% of the patients tested had elevated serum YKL-40, greater than 208 ug/L, patients with high YKL-40, greater than 209 ug/L had a median survival rate significantly shorter than those with a normal serum YKL-40 (para bridging pages 57-58).

One cannot extrapolate the teaching of the specification to the enablement of the claims because Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing an cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to methods of using assay of YKL-40 as a marker to estimate/predict survival expectancy of a cancer

patient. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored prospectively and link those marker results with subsequent histological confirmation of endpoint. This irrefutable link between antecedent marker and subsequent acknowledged disease end-point is the essence of a valid end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). The requirement for validation of the marker is clearly taught by Johansen et al (European J. Of Cancer, Vol 31A, No. 9, pp. 1437-1442) of record, upon which the teachings of the specification drawn to the breast cancer study appears to be based, reveals a comparison of YKL-40 in patients diagnosed with breast CA, wherein survival rates were less for patients with high serum YKL-40, that is at or above 95 percentile of controls, than those with normal serum YKL-40 at the time of entry into the study. The reference further teaches that the sensitivity and specificity of a potential biochemical marker may vary considerably according to different cut-off values and

the authors selected a cut off for serum YKL-40 to 95 percentile of healthy age-matched women (p.1440). In addition, the number of patients in the present study is relatively small and further studies are needed (para bridging pages 1440-1441). Finally, the authors conclude that the study shows for the first time that determination of serum YKL-40 **may** (emphasis added) play an important role ..... for the prognosis of survival in patients suspected of breast cancer recurrence. In particular, the authors (who include Inventor Johansen of the instant application) specifically state that "Longitudinal studies relating serum YKL-40 to progression of breast cancer as well as in other cancer diseases and during different treatment procedures are required". It is clear that this is a pilot study that does not provide enablement for the claimed invention. That the serum determination of YKL-40 may play an important role in survival is not sufficient enablement for the claimed invention in the absence of the studies required by the Johansen et al and Tockman et al which would determine whether or not the claimed invention would actually function as claimed.

Further, the specification clearly teaches the unpredictable nature of the claimed invention on page 55 wherein it is stated that "If preoperative high levels of YKL-40 do prove to identify patients ..... with high risk of recurrence" (which is clearly drawn to reduced survival), wherein the specification makes clear the speculative nature of the claimed invention. In addition, the specification specifically recites that the source of YKL-40 which leads to elevated serum in some colorectal cancer patients is not known but could arise from a variety of sources which are not tumor sources. Finally, the end point of the study was death from all causes. Given

this teaching, it cannot be determined if shortened survival in some or all of the cases studied were due to death from the cancer or from, for example drunk drivers. Further, it cannot be determined whether the elevated YKL-40 was due to the tumor or to other sources. Further, in the absence of the studies required by Johansen et al and Tockman et al, it cannot be determined whether or not elevated expression of YKL-40 can be used to estimate/predict survival expectancy of a cancer patient.

For the same reasons, the data presented drawn to small cell lung carcinoma is not enabling for the claimed invention.

Finally, the specification teaches that the prostate cancer study is a pilot study with an ultimate goal of determining in longitudinal studies what the relationship is between YKL-40 levels and survival. It is clear that at the time the invention was made, the relationship between YKL-40 and survival in prostate cancer was unknown.

Given the teachings of the specification and the art of record, it could not be predicted, with a reasonable expectation of success, that the invention would function as claimed. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

10. Claims 47, 49-51, 54-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of screening for a cancer, selected from the group claimed, in a mammal comprising obtaining a biological sample and measuring YKL-40 in the sample.

The specification teaches that YKL-40 levels can be used as a screening test to detect cancer apparently because a retrospective review of a rheumatoid arthritis study, wherein 15 patients with no evidence of clinically active rheumatoid arthritis were found to develop various cancer types within 5 years after a blood sample was taken. It was found that 12 of these patients had elevated YKL-40 compared to normal controls and developed cancer, whereas 5 patients who also had elevated YKL-40 and inactive rheumatoid arthritis did not develop cancer,. Apparently from these studies, the specification concludes that elevated serum YKL-40 in patients with inactive rheumatoid arthritis can be used to identify patients who are destined to develop clinical symptoms of cancer within 4-5 years (p. 58, lines 5-32). The specification further teaches that serum YKL-40 can identify patients with cancer before clinical symptoms appear wherein cases of anomalous elevations of YKL-40 would merit rigorous follow up tests to determine the location of the cancer. Such tests are not normally carried out on apparently healthy people, but would be justified if serum YKL-40 is elevated (p. 59, lines 4-9).

Applicant admits on the record that in addition to some forms of cancer, diseases known to cause elevation in serum YKL-40 include rheumatoid arthritis and liver disease (p. 60, line 8).

Applicant further teaches that in a group of healthy women, three healthy women whose YKL-40 levels were elevated when monitored for 4 weeks were

found to develop cancer within 2 to 3 years. The study shows that levels of serum YKL-40 can be elevated in healthy subjects well before the cancer which caused the elevation could be detected by clinical symptoms (p. 60, lines 1-17).

One cannot extrapolate the teaching of the specification to the enablement of the claims because no nexus has been established between the elevated YKL-40 in either the arthritis study or the healthy woman study and cancer. Applicant has admitted on the record that both rheumatoid arthritis and liver disease are associated with elevated YKL-40 in serum. Further, Nordenbaek et al (J. Infectious Diseases, 1999, 180:1722-1726) specifically teaches that YKL-40 is elevated in serum of patients with community-acquired penumonia (see abstract); Johansen et al (Arthritis and Rheumatism, 1999,42:2624-2630) specifically teach that levels of YKL-40 is elevated in patients who present with inflammation of the arterial wall (see abstract); Ostergaard et al (Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, 2000, 40:45) teach that YKL-40 is elevated in patients with bacterial meningitis (see abstract); Kronberg et al (Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, 2001, 41:460) specifically teaches that YKL-40 is elevated in serum from patients with pneumoccal bacteria (see abstract); Price et al (WO20000019206) specifically teach that YKL-40 is elevated in pathologies associated with degenerative bone diseases such as rheumatoid arthritis, osteoarthritis, fibrosis, cirrhosis of the liver (see abstract). Given the clear teaching of the large number of pathologies associated with elevated levels of YKL-40, it is not possible to determine or to predict whether the elevated YKL-40 found in the

arthritis patients with inactive rheumatoid arthritis or the healthy woman patients were in any way associated with cancer or whether any of the possible plethora of cases of elevated YKL-40 associated with many different disease states is in any way anomalous. No nexus has been established. Further, given the large variety of sources of overexpressed YKL-40, given the dozens of cancer types that are claimed wherein statistically significant difference between sample and control indicates the presence of that cancer, it cannot be predicted nor would it be expected that the claimed method could distinguish between the various sources of overexpressed YKL-40 to indicate the presence of a specific cancer type. Given the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

11. If Applicant were able to overcome the rejections set forth above, Claims 1-18, 49-51,54-62 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to estimate survival expectancy of a cancer patient, a method of screening for recurrence of a cancer comprising measuring levels of YKL-40 in a fluid sample from a cancer patient, wherein the YKL-40 level is greater than the 95th percentile for normal controls, does not reasonably provide enablement for any of the disclosed methods wherein a sample YKL-40 level in excess of YKL-40 levels in a healthy human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for estimating survival expectancy of a cancer patient/screening for recurrence of a cancer comprising obtaining a biological sample comprising YKL-40 from a cancer patient and comparing the level to the YKL-40 level found in the same sample from a normal healthy human wherein a sample YKL-40 level in excess of YKL-40 levels in the same sample from a normal healthy human indicates a reduced survival expectancy compared to patients with normal YKL-40 level. This includes comparison to any healthy normal human.

The specification teaches in Table 1, p. 45 that YKL-40 levels in normal healthy humans ranges from 60-385 ug/L for women and 57-1015 ug/L in men. The specification further teaches that three healthy women, all of whom were free of any disease known to cause an elevation in serum YKL-40 had elevated levels of YKL-40 and that those levels were well above the 247 ug/L, the 95% level of controls. One cannot extrapolate the teaching of the specification to the enablement of the scope of the claims because, as disclosed above, Johansen et al, 1995, specifically teach that the sensitivity and specificity of a potential biochemical marker may vary considerably according to different cut-off values and the authors selected a cut off for serum YKL-40 to 95 percentile of healthy age-matched women. Finally, US Patent No. 5,726,061, of record, specifically teaches that elevated levels of YKL-40, used to screen for colorectal cancer in patients, must be at least 2-fold higher than an amount of YKL-40 in normal patients. Given the broad range of normal serum YKL-40, it cannot be predicted, nor could it be determined which "normal" healthy human sample could be used to indicate an "elevated" YKL-40. Given the above, no one would consider it more likely than not that the invention would

function as broadly claimed with a reasonable expectation of success. Given the above, it would require undue experimentation to practice the invention as claimed.

12. If Applicant were able to overcome the rejections under 35 USC 101, Claims 38-39 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to screen for a cancer comprising measuring levels of YKL-40 in a fluid sample from a cancer patient, wherein the YKL-40 level is greater than the 95th percentile for normal controls, does not reasonably provide enablement for said method wherein a statistically significant difference in YKL-40 level compared to the sample from a normal healthy mammal indicates the presence of a cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method to screen for recurrence of a cancer comprising measuring levels of YKL-40 in a sample from a cancer patient, wherein the YKL-40 level wherein a statistically significant difference in YKL-40 level compared to the sample from a normal healthy mammal indicates the presence of a cancer. This includes comparison to any normal healthy mammal, any difference, whether elevated or depressed level.

The specification teaches in Table 1, p. 45 that YKL-40 levels in normal healthy humans ranges from 60-385 ug/L for women and 57-1015 ug/L in men. The specification further teaches that three healthy women, all of whom were free of any disease known to cause an elevation in serum YKL-40 had elevated levels of YKL-40 and that those levels were well above the 247 ug/L, the 95% level of controls.

One cannot extrapolate the teaching of the specification to the enablement of the scope of the claims because as disclosed above, Johansen et al, 1995, specifically teach that the sensitivity and specificity of a potential biochemical marker may vary considerably according to different cut-off values and the authors selected a cut off for serum YKL-40 to 95 percentile of healthy age-matched women. Finally, US Patent No. 5,726,061, of record, specifically teaches that elevated levels of YKL-40, used to screen for colorectal cancer in patients, must be at least 2-fold higher than an amount of YKL-40 in normal patients. Given the broad range of normal serum YKL-40, it cannot be predicted, nor could it be determined which "normal" healthy human sample could be used to indicate an "elevated" YKL-40. Further, in each and every exemplified assay of YKL-40 in the specification and in the art of record, association with cancer is always drawn to elevated levels of YKL-40. There is no teaching of any cancer type that has been identified by a reduced expression of YKL-40 or a teaching of how to screen for a cancer comprising assaying for reduced YKL-40. Given the above, no one would consider it more likely than not that the invention would function as broadly claimed with a reasonable expectation of success. Given the above, it would require undue experimentation to practice the invention as claimed.

13. If Applicant were able to overcome the rejections above, claims 1-18, 38-39, 49-51,54-62 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for claimed methods in carcinoma cancers, does not reasonably provide enablement for said methods in the plethora of cancers claimed in claims 1, 38 and 47. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of estimating survival expectancy, screening for recurrence of a cancer, screening for a cancer by measuring a level of YKL-40 in the sample, compared to a normal control, wherein the cancers are selected from the groups recited in claims 1, 38 and 47.

The specification teaches that serum levels of YKL-40 were measured in a clinical group of 60 breast cancer patients (p. 45, lines 10-19), 47 of which entered the study at the time that breast cancer recurrence was first suspected, 6 of whom did not have breast cancer recurrence, 6 had locally advanced disease or distant metastasis at the time of initial breast cancer diagnosis and 7 entered the study after recurrence (p. 26, lines 25-31). Data indicated that a serum YKL-40 level elevated above the 95% level of 120 normal women, correlates to decreased survival in patients with breast cancer (pgs 46-47).

Further, the specification exemplifies a study of serum YKL-40 and colorectal cancer wherein both male and female patients underwent large bowel resection for colorectal cancer (p. 51, lines 6-18) wherein the control samples were taken from persons who were healthy. The number of patients with YKL-40 levels above the age corrected 95th percentile of normal controls was 159, wherein the level is 247 ug/L wherein a significant correlation of serum level with age was found (p. 52, lines 1-12). A strong association was found between short survival and high preoperative YKL-40 levels and there was a significant relation between serum YKL-40 and Dukes' stage. Applicant further states that "If preoperative high levels

of YKL-40 **do prove** (emphasis added) to identify patients in Dukes' B and C with a high risk of recurrence, more intensive follow-up and treatment could be given to these patients". Further, the source of YKL-40 which lead to elevated serum levels of protein in some colorectal cancer patients is not known but could arise from secretion by the tumor cells themselves, from secretion by inflammatory cells and from normal cells in areas of the colon adjacent to tumor (p. 55, lines 14-19). Further, preliminary data investigating the expression of YKL-40 in colon cancer biopsies show that some cancers stain intensely for YKL-40 while others are completely negative (p. 55, lines 14-19). If elevated levels of serum YKL-40 do primarily reflect secretion from a subset of colorectal tumors, then the poor prognosis of patients with elevated serum YKL-40 suggests that YKL-40 expression may be associated with the ability of a tumor cell to invade normal tissues and to metastasize to distant sites (para bridging pages 55-56). The endpoint of the study was death of all causes (p. 52, line 28).

Further, the specification exemplifies the elevation of YKL-40 levels in prostate cancer wherein a pilot study was established to determine whether YKL-40 is elevated in prostate cancer with the ultimate goal of measuring serum YKL-40 in longitudinal studies of patients with prostate cancer in order to determine the precise relationship between YKL-40 levels and survival, wherein 8 of 20 patients have serum YKL-40 levels above 247 ug/L, Based these results, analysis will be undertaken of serum YKL-40 from past longitudinal studies of patients in which survival is known (p. 56, lines 16-27).

The specification exemplifies the elevation of YKL-40 levels in small cell lung carcinoma patients wherein 40% of the patients tested had elevated serum YKL-40, greater than 208 ug/L, patients with high YKL-40, greater than 209 ug/L had a median survival rate significantly shorter than those with a normal serum YKL-40 (para bridging pages 57-58).

One cannot extrapolate the teaching of the specification to the scope of the claims because each of the exemplified cancer types is a carcinoma. In particular, Guinan et al (Urology, 1975, 6:693-696) specifically teaches adenocarcinoma of the prostate (see abstract); Veronesi et al (Lancet, 1997, 349:1864-1867) specifically teaches breast carcinoma (see abstract); Moertel et al (J. Natl Can Inst., 1975, 54:69-71) specifically teaches colorectal carcinoma (see abstract); and Joasson et al (Nouvelle Presse Medicale, 1979, 8:3665) specifically teaches small cell lung carcinoma (see abstract). Although it is reasonable to assume that cancer cells with a common tissue type, in this case epithelial cells, would have a similar mechanism of carcinogenesis with similar markers, the heterogeneity of different cancer types in terms of etiology and markers is well known in the art . For example, Osband and Ross (Immunology Today, 1990, 11:193-195) teach that there is an obvious heterogeneity of tumors in terms of the biochemistry, antigenicity and metastatic potency of neoplastic cells (p. 194, para 2), so that even if one type of cancer exhibits perturbation of YKL-40, it cannot be predicted, nor would it be expected that the same pattern of perturbation will be present in all tumor types. Based on the information in the specification and known in the art, one of skill in the art would not expect to be able to predict in which tumor types, other than carcinoma, the

invention would function as claimed with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

14. It is noted that an IDS was submitted on October 7, 2002. However, a review of the file failed to disclose any other the papers listed other than 5,726,061, WO 95/01995 and Johansen et al, 1995, all of which appear to have been previously submitted. If Applicant wants the listed papers to be considered, they must be submitted along with the IDS form.

15. No claims allowed.

16. All other objections and rejections recited in Paper No. 30 are withdrawn.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this

application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
April 8, 2003